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Effects of Renal Sympathetic Denervation on Arterial Stiffness and Central Hemodynamics in Patients With Resistant Hypertension

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Objectives This study investigated the effect of catheter-based renal sympathetic denervation (RD) on central hemodynamics in patients with resistant hypertension.

Background High central blood pressure (BP) increases cardiovascular events and mortality independently of peripheral BP. The effect of RD on central BP is unclear.

Methods A total of 110 patients underwent bilateral RD. Radial artery applanation tonometry and pulse wave analysis were used to derive central aortic pressure and hemodynamic indices at baseline and 1, 3, and 6 months after ablation. Ten patients with resistant hypertension not undergoing RD served as controls.

Results RD significantly reduced mean central aortic BP from 167/92 mm Hg to 149/88 mm Hg, 147/85 mm Hg, and 141/85 mm Hg at 1, 3, and 6 months ($p < 0.001$), respectively. Aortic pulse pressure decreased from 76.2 ± 23.3 mm Hg to 61.5 ± 17.5 mm Hg, 62.7 ± 18.1 mm Hg, and 54.5 ± 15.7 mm Hg 1, 3, and 6 months after RD ($p < 0.001$), respectively. Six months after RD aortic augmentation and augmentation index were significantly reduced by −11 mm Hg ($p < 0.001$) and −5.3% ($p < 0.001$), respectively. Carotid to femoral pulse wave velocity showed a significant reduction from 11.6 ± 3.2 m/s to 9.6 ± 3.1 m/s at 6 months ($p < 0.001$). Consistently, ejection duration and aortic systolic pressure load were significantly diminished, indicating improvement of cardiac work load by RD. No significant changes were obtained in control patients.

Conclusions Besides the known effect of RD on brachial blood pressure, the study showed for the first time that this novel approach significantly improves arterial stiffness and central hemodynamics, which might have important prognostic implications in patients with resistant hypertension at high cardiovascular risk. (J Am Coll Cardiol 2012; 60:1956–65) © 2012 by the American College of Cardiology Foundation

Arterial hypertension affects more than one-quarter of the adult population worldwide (1). Despite broad availability of effective pharmaceutical agents, a substantial proportion of hypertensive patients do not reach blood pressure (BP) targets (2,3). Therapy refractory hypertension is a major risk factor for myocardial infarction, stroke and mortality (2,4). Renal sympathetic nerves are crucial for the development and maintenance of arterial hypertension by regulating renin release, tubular sodium reabsorption, and renal blood flow (5). To reduce renal sympathetic afferent and efferent activity, a novel percutaneous, catheter-based approach directly targeting the renal sympathetic nerves by applying endovascular radiofrequency energy in the renal arteries has been developed (6). In a multicenter, randomized trial this minimally invasive procedure effectively reduced systolic blood pressure (SBP) and diastolic blood pressure (DBP) measured over the brachial artery in patients with resistant hypertension (7).

Conventional brachial cuff BP measurements are widely assumed to accurately reflect pressures in the central circulation. This assumption is supported by consistent observations that brachial BP values are powerful predictors of cardiovascular events, morbidity, and mortality (4). However, central aortic pressure parameters and left ventricular load are determined not only by cardiac output and peripheral vascular resistance but also by the stiffness of conduit arteries and the timing and magnitude of pressure wave reflections (8,9). Increasing evidence indicates that aortic pulse wave velocity (PWV), which is inversely related to

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distensibility, and central augmentation index (AIx), a composite measure that depends on the site and degree of reflection, are independent predictors of cardiovascular structural damage and clinical outcomes (10–15). Furthermore, central BP may be differentially affected by antihypertensive drugs, despite a similar reduction of brachial BP, which was suggested to explain different drug effects on clinical endpoints (16). The impact of renal catheter ablation on PWV and AIx is unclear. Therefore, we evaluated whether this new therapeutic approach, besides lowering brachial BP, has a positive effect on central hemodynamic in patients with resistant hypertension.

Abbreviations and Acronyms

AIx = augmentation index
BP = blood pressure
DBP = diastolic blood pressure
MBP = mean blood pressure
PWV = pulse wave velocity
PWV_{cf} = carotid to femoral pulse wave velocity
RD = renal sympathetic denervation
SBP = systolic blood pressure

Methods

The study was approved by the local ethic committees in accordance with the Declaration of Helsinki. Patients were treated between October 2009 and September 2011 with subsequent follow-up for 6 months. All patients provided written informed consent.

Study subjects. Eligible patients were older than 18 years and had an office BP of ≥160 mm Hg (≥150 mm Hg for type 2 diabetics) or more, despite treatment with at least 3 antihypertensive drugs, with no changes in medication for a minimum of 3 months prior to enrollment. To exclude white coat hypertension, 24-h BP recordings and home BP protocols were consulted in addition to office BP measurements at the hospital before enrollment. Patients with secondary causes of hypertension were excluded. Further exclusion criteria were renal insufficiency with an estimated glomerular filtration rate ≤45 ml/min/1.73 m^2 (using the simplified Modification of Diet in Renal Disease formula) (17), renal artery anatomy ineligible for treatment (main renal arteries <4 mm in diameter or <20 mm in length, hemodynamically or anatomically significant renal artery stenosis or abnormality in either renal artery, a history of prior renal artery intervention including balloon angioplasty or stenting, multiple main renal arteries in either kidney), pregnancy, type 1 diabetes mellitus, hemodynamically significant valvular heart disease, unstable angina, or myocardial infarction or stroke within the last 6 months before enrollment (7,18,19). One hundred and ten patients underwent renal denervation and 10 patients were in the control group. In all patients the same inclusion/exclusion criteria were applied as part or extension of the randomized controlled Symplicity HTN-2 protocol (NCT00888433) (7).

Hemodynamic. Prior to BP measurements drug adherence was ensured via interview and by reviewing home BP protocols. Blood pressure and heart rate were recorded after 10 min of supine rest using an automatic oscillometric monitor (Omron HEM-705, Omron Healthcare, Vernon Hills, Illinois) on the brachial artery. Blood pressure was measured on the same side throughout the study. Averages of triplicate measurements with 1-min intervals were used for analysis. Mean blood pressure (MBP) was calculated from SBP and DBP as: MBP = DBP + 0.4(SBP − DBP) (20).

For assessments of arterial stiffness, a commercially available applanation tonometer (SphygmoCor, AtCor Medical Ltd, Sydney, Australia) was used in connection with analysis software (version 8.0, SphygmoCor Cardiovascular Management Suite), as previously described (11). In short, peripheral radial artery waveforms were recorded using a high-fidelity micromanometer (Millar Instruments, Houston, Texas). Recorded pressure waveforms were calibrated to the statistic mean of 3 successive brachial cuff BP measurements recorded on the same arm immediately before applying the tonometer (see previous). After 30 to 45 s of recording duration, a validated mathematical transfer function (21,22) was applied to generate the central aortic waveform. The inflection point representing the merging point of the incident and the reflected pressure wave was calculated and used to quantify the augmentation pressure. The augmentation index (AIx) was defined as the augmentation pressure expressed as percentage of the aortic pulse pressure. To minimize the influence of heart rate on AIx, the AIx corrected for a heart rate of 75 beats/min was derived (23). Only recordings of sufficient quality with device-generated operator index values above 80 (maximum of 100) were used for analysis.

Carotid to femoral pulse wave velocity (PWV_{cf}) was measured with the same device by sequentially recording electrocardiogram-gated arterial waveforms at the femoral and carotid arteries, as previously described (24). PWV_{cf} was calculated by dividing the pulse wave travel distance by the pressure wave transit time. The pulse wave travel distance was assessed by subtracting the distance from the suprasternal notch to the carotid artery recording site from the suprasternal notch to the femoral artery recording site, resulting in best correspondence with invasively measured aortic PWV (20,25). To minimize intraindividual variability, pulse wave velocity was measured 2 times during every visit and the average of both recordings was used for statistical analysis. Reference values for PWV corrected for MBP according to age categories were calculated on the basis of the regression equations recently suggested (20). The clinical assistant trained and specialized to perform the recordings of central waveforms was blinded to the treatment allocation of the patients.

Renal denervation procedure. Renal angiograms were performed via femoral access to confirm anatomic eligibility. In the same session, the treatment catheter (Symplicity and Flex by Ardian Inc., Palo Alto, California) was introduced into each renal artery using a guiding catheter. Up to 6 ablations at 8 W for 2 min each were performed in both

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renal arteries. Treatments were delivered from the first distal main renal artery bifurcation to the ostium proximally and were spaced longitudinally and rotationally under fluoroscopic guidance. Catheter tip impedance and temperature were constantly monitored, and radiofrequency energy delivery was regulated according to a predetermined algorithm. Visceral pain at the time of energy delivery was managed with intravenous analgetics and sedatives. Heparin was given to achieve an activated clotting time during the procedure of more than 250s.

Statistical analysis

Data are presented as mean ± SD. Differences in the mean values were compared using a 2-tailed *t* test for continuous variables and Fisher-Yates testing for nominal variables. Changes of all parameters with multiple measurements including p value for statistical trend were analyzed from baseline to 1, 3, and 6 months by 2-factor analysis of variance for repeated measurements. The Scheffé correction algorithm was used to compute post hoc comparisons of significant values. A comparison between linear trends in the treatment group for patients with complete data of all follow-ups and the control group was performed using the group square linear trend interaction test. A p value <0.05 was considered statistically significant. All statistical analyses were performed with SPSS statistical software (version 12.0, SPSS Inc., Chicago, Illinois).

Results

One hundred and twenty patients were included in the study; 110 underwent renal sympathetic denervation (RD), 10 patients served as control. Most patients in the treatment group were male (70%). The mean age was 63.6 ± 9.9 years. On average, patients were taking 4.8 antihypertensive drugs. All patients were maintained on baseline antihypertensive medication during the study period. The patient demographic and clinical characteristics did not differ between the RD and control groups (Table 1).

At baseline, overall mean sitting office SBP in the treatment group was 181.0 ± 24.7 mm Hg and mean sitting office DBP was 91.4 ± 12.8 mm Hg with a heart rate of 63.4 ± 11.9 beats/min. Ablation of the renal arteries was performed without any complications in all patients. Figure 1 shows representative averaged radial artery waveforms and the resulting derived central aortic waveforms from an individual patient at baseline and 1 month after renal denervation. There are clear differences in the morphology of both the radial and central aortic waveforms. Renal denervation resulted in a reduction of the systolic peak pressures, a narrower peripheral and central waveform, and an attenuation of the late systolic peak in the central aortic waveform. Consistently, mean brachial systolic and diastolic pressure, and derived central aortic systolic and diastolic pressure were already significantly reduced 1 month after the procedure, and further declined throughout the 6 months follow-up (n = 59 at 3 months, n = 55 at 6 months) (Fig. 2, Table 2). Renal denervation also significantly decreased peripheral and central aortic pulse pressures (Fig. 3, Table 2). There was no significant change in control patients (n = 10 throughout 6 months) (Figs. 2 and 3, Table 2).

Table 1 Baseline Characteristics

	RD	Control	p Value
Group size (n)	110	10	
Age, yrs	63.6 ± 9.9	65.2 ± 7.7	0.489
Male	77 (70%)	8 (80%)	0.324
BMI, kg/m^2	29.4 ± 4.5	29.8 ± 3.6	0.748
Coronary artery disease	22 (20%)	3 (30%)	0.927
Atrial fibrillation	16 (14.5%)	1 (10%)	0.973
Stroke	17 (15.5%)	1 (10%)	0.956
Type 2 diabetes	39 (35.5%)	4 (40%)	0.782
Hypercholesterolemia	66 (60%)	7 (70%)	0.403
Smoking	27 (24.5%)	2 (20%)	0.625
Number of antihypertensive drugs	4.8 ± 2.1	5.6 ± 1.9	0.189
Patients receiving (drug classes)			
ACE inhibitors/ARBs	100 (91%)	10 (100%)	0.937
Direct renin inhibitors	43 (39%)	4 (40%)	0.396
Beta-blockers	95 (86%)	9 (90%)	0.838
Calcium-channel blockers	76 (70%)	7 (70%)	0.653
Diuretics	90 (82%)	9 (90%)	0.416
Sympatholytics	41 (37%)	4 (40%)	0.584

Values are mean ± SD or n (%).
ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; BMI = body mass index; DBP = diastolic blood pressure; RD = renal denervation; SBP = systolic blood pressure.

Central aortic systolic pressure wave augmentation was markedly attenuated after the procedure but not in the control group (Fig. 4, Table 2). Renal denervation also significantly decreased AIx and AIx corrected for a heart rate of 75 beats/min during follow-up (Fig. 4, Table 2). Furthermore, both the ejection duration corrected for the cycle length and the SBP load assessed by the systolic pressure-time integral were diminished by the intervention, indicating a reduction of cardiac systolic work load, while these parameters remained unchanged in control patients (Table 2).

To obtain the impact of the efficacy of lowering office BP by RD on central aortic pressures, we separately evaluated patients with office SBP reduction above and below the median of −18 mm Hg at 1 month. Expectedly, in those patients with greater BP decrease improvement of all central hemodynamic parameters was more pronounced (Table 3). Twenty-two patients achieved a resting SBP of <140 mm Hg at 6 months follow-up and were newly controlled. In these patients central aortic systolic (121.9 ± 8.9 mm Hg), diastolic (76.7 ± 8.6 mm Hg), and pulse pressure (44.0 ± 8.0 mm Hg) were also within the age-corrected normal range 6 months after RD. Notably, the degree of BP reduction following RD appeared to correlate with the severity of initial hypertension. In patients with BP values above the median office SBP of 177 mm Hg, the reduction after RD was significantly larger than in those with lower initial SBP values (peripheral SBP −24.7 ± 20.9 mm Hg after 1 month vs.

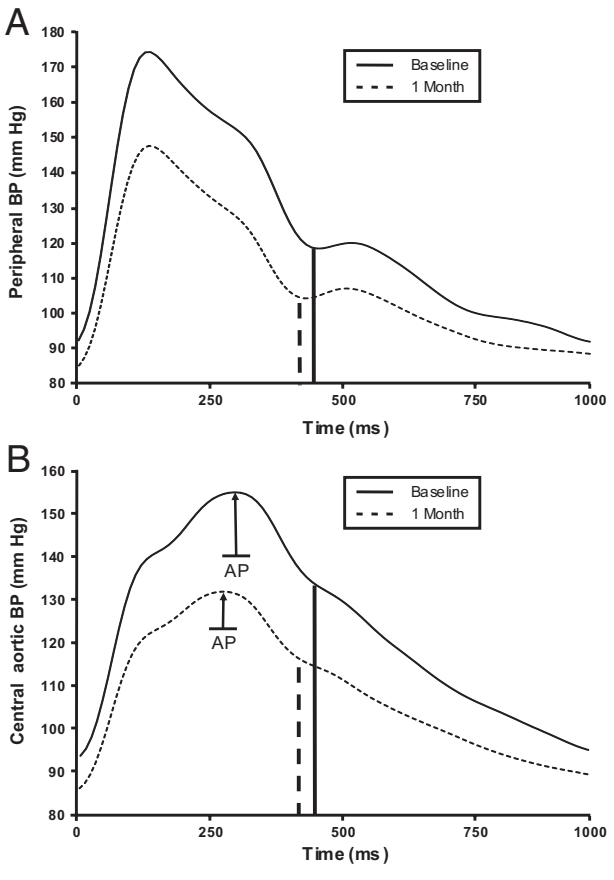

Figure 1 **Effect of RD on Peripheral and Central Aortic Waveforms**

Examples of peripheral **(A)** and corresponding derived central aortic **(B)** waveforms at baseline **(solid line)** and 1 month after RD **(broken line)**. In both panels the dicrotic notch **(incision)** caused by the closure of the aortic valve is visible, representing the division between systole and diastole **(vertical lines)**, the leftward shift demonstrating a reduction of the ejection duration 1 month after renal denervation (RD) compared with baseline. The aortic augmentation pressure (AP) from the reflected wave was calculated as the difference between central peak systolic pressure and the pressure at the inflection point representing the onset of the reflected wave from the peripheral vascular bed **(arrows)**. Following RD peripheral and aortic pressure waveforms show a marked reduction of the systolic (maximum) and diastolic (minimum) pressure, pulse pressure (distance between minimum and maximum), and AP **(arrows)**. BP = blood pressure.

−6.0 ± 12.5 mm Hg, $p < 0.001$; central SBP −21.5 ± 23.8 mm Hg vs. −5.9 ± 10.7 mm Hg, $p = 0.004$).

To assess arterial stiffness we measured PWV_{cf}, which is considered the gold standard to determine aortic PWV noninvasively (10,20). Renal denervation significantly reduced PWV_{cf} at 1, 3, and 6 months by −0.97 ± 4.3 m/s ($p = 0.053$), −1.87 ± 3.8 m/s ($p = 0.002$), and −2.0 ± 4.0 m/s ($p = 0.001$), respectively (Fig. 5, Table 2). The intraindividual variation of PWV_{cf} remained constant throughout the follow-up with average standard error values of PWV_{cf} recordings being 0.89 ± 0.63 m/s at baseline, 0.87 ± 0.56 m/s at 1 month, 0.88 ± 0.61 m/s at 3 months, and 0.88 ± 0.69 m/s at 6 months. Reference values for PWV_{cf} remain controversial (20). The ESC/ESH guidelines proposed a fixed cutoff PWV_{cf} value of 9.6 m/s (12 m/s with directly measured distance) (26). Improvement of PWV_{cf} by RD in those patients with a baseline PWV_{cf} >9.6 m/s ($n = 46$) was more pronounced compared to the total RD group with a reduction of −2.4 ± 2.7 m/s ($p = 0.001$), −2.5 ± 4.5 m/s ($p < 0.001$), and −2.9 ± 4.1 m/s ($p < 0.001$) at 1, 3, and 6 month follow-up, respectively (Fig. 5). Because age modifies PWV_{cf} (20,27), we additionally evaluated age-corrected values. In patients with baseline PWV_{cf} exceeding the double standard deviation of normal values of their age category (20) ($n = 37$), PWV_{cf} decreased by −2.9 ± 3.1 m/s ($p = 0.002$), −3.6 ± 4.3 m/s ($p = 0.002$), and −4.0 ± 3.6 m/s ($p = 0.004$) 1, 3, and 6 months after the procedure, respectively (Fig. 5).

Given that PWV at any age is linearly related to BP (20), we aimed to estimate whether RD might have any effect on PWV_{cf} beyond BP reduction. Therefore, we analyzed the difference between the predicted PWV corrected for the MBP according to age categories on the basis of the regression equations recently derived from a large reference population (20). At baseline age- and MBP-corrected predicted PWV was identical to the measured PWV_{cf} values of our population ($\Delta PWV_{cf} - PWV_{predicted}$ −0.01 ± 4.75 m/s, p = NS). However, 1, 3, and 6 months after renal denervation actually measured PWV_{cf} was significantly lower than the predicted parameters ($\Delta PWV_{cf} - PWV_{predicted}$: 1 month −1.04 ± 2.25 m/s, $p = 0.038$; 3 months −1.68 ± 2.57 m/s, $p < 0.001$; 6 months −1.44 ± 2.44 m/s, $p = 0.005$), suggesting a possible additional BP-unrelated effect of the intervention over time. In addition, to assess the changes of PWV_{cf} independent of BP changes, we evaluated the ratios of the ΔPWV_{cf} to the change in MBP (ΔMBP), as previously reported (28,29). After RD the $\Delta PWV_{cf}/\Delta MBP$ ratio increased in the total treatment group (7.5 ± 15.9 vs. 9.3 ± 19.5, p = NS) and in patients with baseline PWV_{cf} exceeding the double standard deviation of normal values (14.9 ± 17.5 vs. 26.9 ± 34.3, $p < 0.001$) from 1 month to 6 months, respectively.

Discussion

Besides the known effect of renal denervation on brachial BP (6,7), our study showed for the first time that this novel approach significantly improves central hemodynamics. Increasingly it is being acknowledged that central aortic BP, which is the pressure exerted on the heart and brain, may be different from the pressure that is measured at the arm, as the reflected wave is added to a different part of the waveform (30). Notably, clinical studies have indicated that central BP may have predictive value independent of traditional risk factors and particularly independent of the corresponding peripheral (i.e., brachial BP) (10–15,31). Among markers of central hemodynamic arterial stiffness, aortic pulse pressure, augmentation pressure, and augmentation index have proven to be important parameters for the

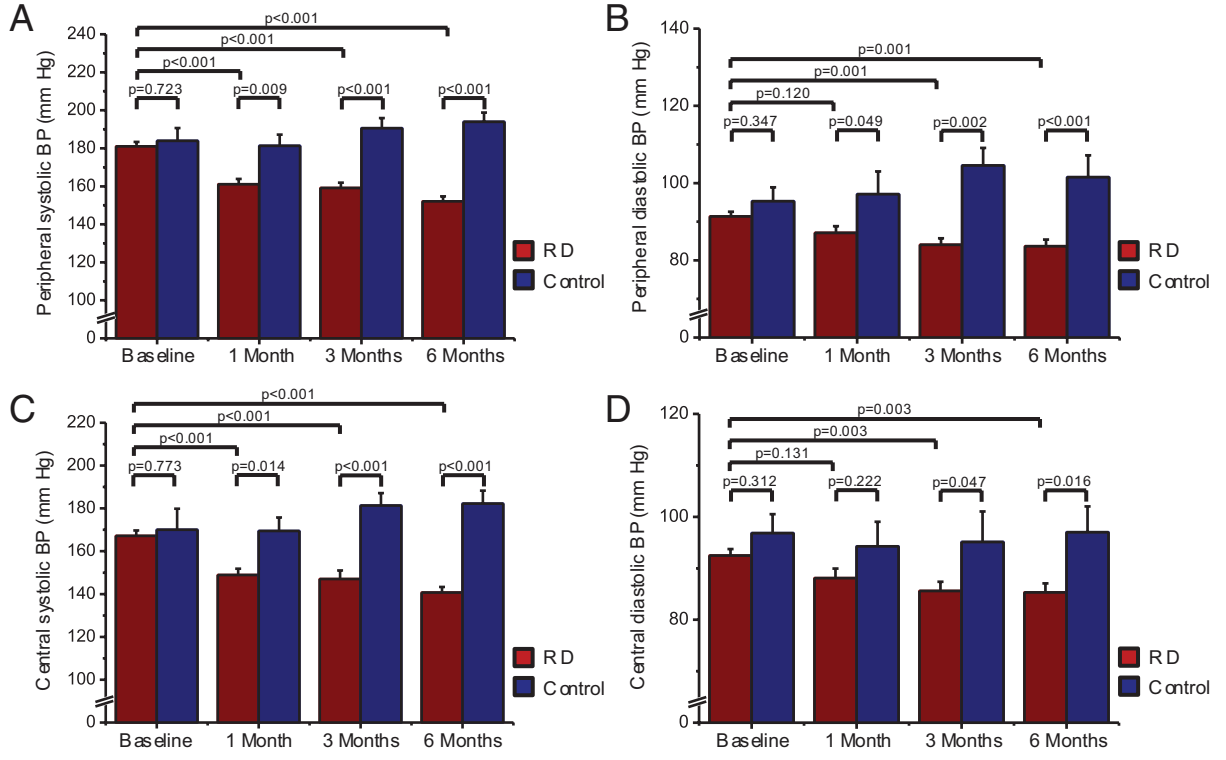

Figure 2 **Effect of RD on Peripheral and Central BP**

Peripheral brachial systolic **(A)** and diastolic blood pressure (BP) **(B)**, and derived central aortic systolic **(C)** and diastolic BP **(D)** at baseline and 1, 3, and 6 months after renal denervation (RD) versus control patients (mean ± SEM).

assessment of cardiovascular risk and mortality (10,11,31), which all were positively affected by RD in our patients with resistant hypertension.

Blood pressure reduction, per se, is the major determinant of the benefit of antihypertensive treatment. This has been shown in several placebo-controlled trials, trials that compared more intensive versus less intensive BP-lowering strategies, and trials comparing different active regimens (26,32). However, despite a similar peripheral BP decrease central hemodynamics may be differentially affected by various classes of BP-lowering drugs depending on their mode of action (16,33,34). Experimental and clinical data have shown beneficial effects on central aortic BP, augmentation pressure, and PWV for angiotensin-converting enzyme inhibitors (35), angiotensin-1 receptor blockers (35,36), calcium antagonists of the dihydropyridine type, and alpha-adrenergic blockers (35,37). Notably, for beta-blockers an adverse effect on central hemodynamics was obtained during short-term administration (35), and the reduction of central aortic pressure and augmentation during long-term therapy was markedly smaller than for other antihypertensive classes (16,33,34,37), which was attributed to the reduction of heart rate by beta-blockers (37,38). Due to the nature of resistant hypertension patients in our study were treated with a combination of the most common antihypertensive drug classes. The fact that arterial stiffness, aortic pulse pressure, augmentation pressure, and augmentation index were positively affected by RD in addition to effects of this extensive medication supports the notion of a synergistic action of RD and antihypertensive drugs on central hemodynamics.

While the most pronounced effect on central hemodynamics was obtained after 1 month, there was an additional continuous effect of RD both on BP and central hemodynamics throughout the 6-month follow-up. Renal denervation is likely to decrease BP mainly by diminishing peripheral vascular resistance. However, as indicated previously several parameters besides arterial stiffness such as heart rate, ejection duration, and stroke volume affect central hemodynamics, making the definition of RD-related mechanisms more complex. Slower heart rate generally results in prolongation of systolic ejection time, a delay of the peak of the outgoing pressure wave, and thereby an increased likelihood that pressure wave reflections will augment the outgoing wave during systole, with ejection time being the strongest independent correlate for augmentation index in some reports (39). In previous studies RD moderately decreased heart rate by −3.8 to −4.0 beats/min at 3 months, which was nonsignificant in some and statistically significant in other reports (18,40). In the present study RD

Table 2 Hemodynamic and Pulse Wave Analysis Parameters in RD and Control Patients at Baseline, 1, 3, and 6 Months

	RD (n = 110)					Control (n = 10)					
	Baseline	1 Month	3 Months	6 Months	p Value for Trend (n = 55)	Baseline	1 Month	3 Months	6 Months	p Value for Trend (n = 10)	p Value for RD Versus Control at 6 Months
Basic hemodynamic parameters											
Resting SBP, mm Hg	181.0 ± 24.7	161.1 ± 22.8	159.1 ± 22.1	152.1 ± 20.0	<0.001	183.9 ± 21.6	181.3 ± 18.5	190.6 ± 16.9	193.9 ± 15.4	0.491	<0.001
Resting DBP, mm Hg	91.4 ± 12.8	87.0 ± 14.0	84.0 ± 13.1	83.7 ± 13.5	0.0026	95.3 ± 11.5	97.1 ± 18.9	104.6 ± 15.6	101.5 ± 17.9	0.251	<0.001
Peripheral PP, mm Hg	89.3 ± 21.5	73.9 ± 17.6	73.9 ± 20.0	67.7 ± 15.8	<0.001	88.8 ± 25.0	84.2 ± 15.2	83.2 ± 14.9	92.4 ± 16.8	0.308	<0.001
Heart rate at rest, beats/min	63.4 ± 11.9	60.4 ± 9.4	59.9 ± 9.5	59.4 ± 10.4	0.0001	58.2 ± 8.1	57.2 ± 5.2	56.7 ± 7.5	60.1 ± 7.0	0.160	0.840
Central hemodynamic parameters											
Central SBP, mm Hg	167.2 ± 26.4	148.9 ± 23.8	147.0 ± 24.0	140.7 ± 20.5	<0.001	170.0 ± 31.2	169.5 ± 20.0	180.5 ± 17.5	182.3 ± 19.2	0.501	<0.001
Central DBP, mm Hg	92.5 ± 13.3	88.1 ± 14.6	85.3 ± 13.2	85.3 ± 13.6	<0.001	96.9 ± 11.6	94.3 ± 15.2	95.1 ± 18.8	97.0 ± 15.8	0.633	0.016
Central PP, mm Hg	76.2 ± 23.3	61.5 ± 17.5	62.7 ± 18.1	54.5 ± 15.7	<0.001	78.6 ± 26.9	75.7 ± 22.3	85.4 ± 23.6	84.3 ± 24.7	0.715	<0.001
Augmentation, mm Hg*	26.0 ± 12.7	20.0 ± 9.5	18.8 ± 11.2	15.5 ± 7.9	<0.001	30.6 ± 12.7	30.3 ± 12.0	33.5 ± 11.8	34.6 ± 12.9	0.284	<0.001
Augmentation index, %	32.7 ± 9.0	30.4 ± 9.2	27.9 ± 11.1	27.4 ± 9.7	<0.001	37.7 ± 4.2	38.9 ± 5.3	38.5 ± 4.3	37.3 ± 5.7	0.382	0.006
Augmentation index @ 75 beats/min, %†	27.0 ± 8.2	23.9 ± 9.2	21.0 ± 10.1	20.3 ± 8.7	<0.001	29.2 ± 3.7	29.9 ± 5.7	28.5 ± 4.3	29.4 ± 5.5	0.626	0.002
Ejection duration, ms	332.9 ± 30.1	329.9 ± 26.2	331.6 ± 29.8	330.4 ± 31.8	0.092	329.3 ± 32.0	334.5 ± 34.4	330.5 ± 30.8	334.9 ± 32.5	0.589	0.681
Ejection duration, % CL‡	34.6 ± 4.8	33.0 ± 4.1	32.9 ± 3.5	32.5 ± 4.5	0.002	31.6 ± 4.2	31.3 ± 4.3	29.7 ± 30.8	31.1 ± 2.6	0.545	0.330
Pressure-time integral systolic, mmHg · s§	2,982.7 ± 605.1	2,621.4 ± 605.7	2,580.8 ± 505.2	2,483.0 ± 544.1	<0.001	2,879.6 ± 354.8	2,788.5 ± 557.4	2,763.5 ± 315.8	2,911.9 ± 255.2	0.815	0.038
PWV_{cf}, m/s	11.58 ± 3.2	10.61 ± 2.8	9.71 ± 2.6	9.58 ± 3.1	<0.001	11.88 ± 4.3	12.32 ± 2.0	11.36 ± 2.3	12.58 ± 3.1	0.256	0.006
Laboratory tests											
Serum creatinine, mg/dl	1.02 ± 0.67	0.98 ± 0.21	1.06 ± 0.38	0.93 ± 0.32	0.213	0.97 ± 0.25	1.02 ± 0.28	0.93 ± 0.34	0.96 ± 0.38	0.256	0.836
GFR, ml/min/1.73 m^2	81.6 ± 24.2	84.4 ± 31.4	88.1 ± 34.5	86.3 ± 27.2	0.786	84.5 ± 21.5	88.3 ± 23.1	90.4 ± 21.2	87.3 ± 22.1	0.812	0.414

Values are mean ± SD. *Augmentation (ΔP) is the difference between maximal pressure and incident pressure at the first peak. †Augmentation index is proportion of the central pressure wave height attributable augmentation (ΔP) (AIx = (ΔP/PP) × 100) corrected for a heart rate of 75 beats/min. ‡Ejection duration was measured from start of waveform to closure of the aortic valve (see incision in Fig. 1) corrected for the cycle length (CL). §Systolic pressure-time integral is integration of the area under the central pulse pressure (PP) curve during ejection duration.

DBP = diastolic blood pressure; GFR = glomerular filtration rate; PWV_{cf} = carotid to femoral pulse wave velocity; RD = renal denervation; SBP = systolic blood pressure.

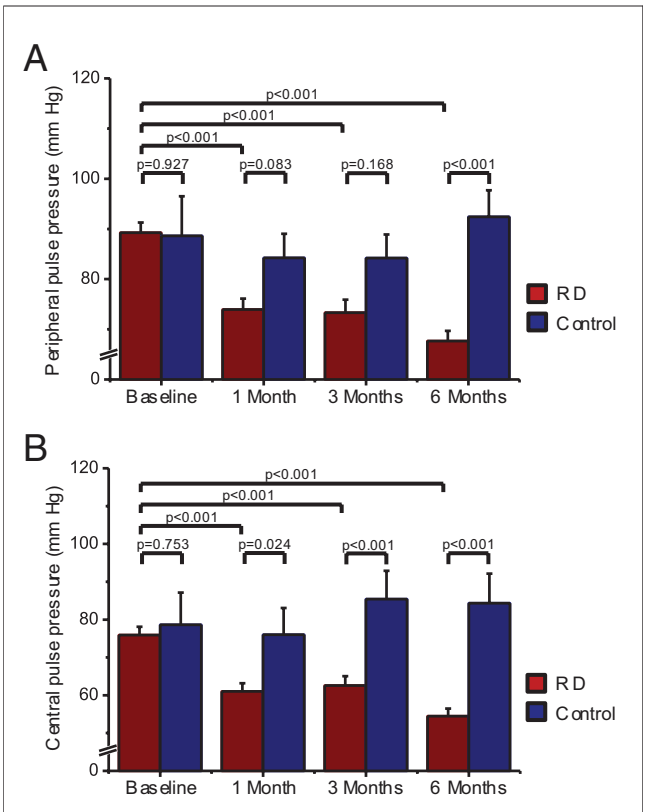

Figure 3 **Effect of RD on Pulse Pressure**

Peripheral brachial **(A)** and central aortic pulse pressure **(B)** at baseline and 1, 3, and 6 months after renal denervation (RD) versus control patients (mean ± SEM).

reduced heart rate to a similar extent (i.e., −3.5 and −4.0 beats/min at 3 and 6 months, respectively. Notably, unlike instances in which heart rate inversely correlates to ejection time such as pacing, drug interventions, and exercise (22,23,39,41,42), RD did not significantly prolong ejection duration and diminished heart rate corrected ejection time, which possibly might account for the substantial improvement of central hemodynamics by RD despite lowering heart rate.

Given that for resistant hypertension per definition no reasonable further pharmaceutical options are available, the effect of RD on central hemodynamics at present may not be compared with other treatment strategies. Nevertheless we aimed to assess whether RD might exert any additional effect on central hemodynamics beyond reduction of office BP in our patients with resistant hypertension. Therefore, we evaluated the difference between the predicted PWV corrected for age and MBP as recently suggested (20), and the measured values for every individual patient at baseline and after RD. At baseline predicted and real PWV values were identical: 1) validating the proposed equations in our patient cohort; and 2) supporting accuracy of the measurements. Notably, after RD actual PWV measures were lower than the predicted age- and MBP-corrected values; while this intraindividual decrease on top of BP reduction was small, differences still reached statistical significance. In addition, we obtained an increase of the $\Delta PWV_{cf}/\Delta MBP$ ratio after RD particularly in patients with high baseline PWV_{cf} (28,29). Moreover, in patients with a reduction of office SBP below the median (Table 3), although there was minimal decrease in central pressure, the reduction in PWV_{cf} was comparable to that seen in the group with pronounced office and central pressure response after RD. These data further support the notion that RD might exert BP-independent effects on arterial stiffness, and might indicate dissociation between reduction in arterial stiffness and wave reflections in systole.

Cardiac afterload and thereby cardiac systolic work load increase directly with a reduction in elastic distensibility and indirectly with a faster backward propagation of pulse wave reflections from the peripheral vascular bed (43,44). In patients with hypertension and heart failure with a preserved ejection fraction vascular stiffness and elevated systolic afterload have been implicated to play an important role in the pathophysiology of diastolic dysfunction (45–47). In the present study RD significantly diminished cardiac systolic work load as evident by shorter ejection duration and reduced SBP load after the procedure. Notably, similar to a decrease in PWV_{cf}, reductions in these parameters related to

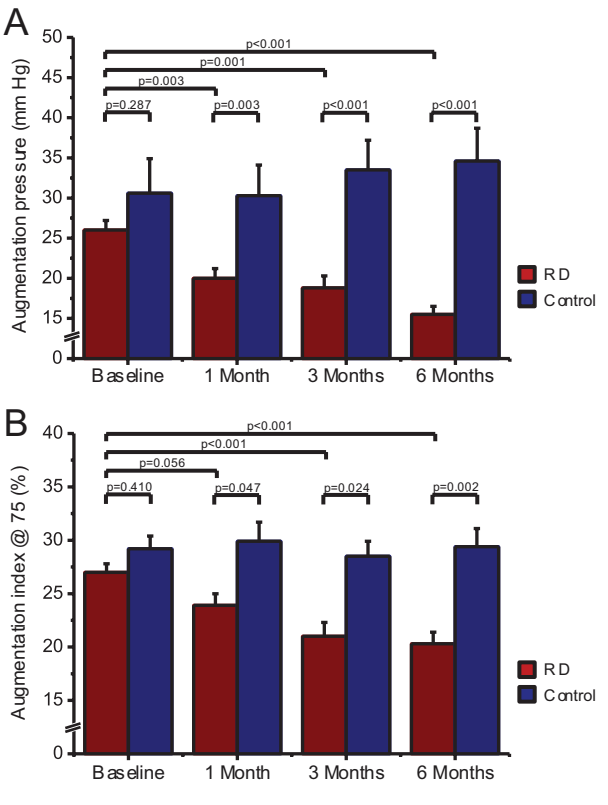

Figure 4 **Effect of RD on Augmentation Pressure**

Central aortic augmentation pressure **(A)** and augmentation index corrected for a heart rate of 75 beats/min **(B)** at baseline, and 1, 3, and 6 months after renal denervation (RD) versus control patients (mean ± SEM).

Table 3 Hemodynamic and Pulse Wave Analysis Parameters in Patients With Office SBP Reduction Above or Below the Median of 18 mm Hg at 1 Month After Renal Denervation

	SBP Reduction <18 mm Hg		SBP Reduction >18 mm Hg	
Parameter	Change Versus Baseline	p Value	Change Versus Baseline	p Value
Peripheral SBP, mm Hg	−4.2 ± 7.8	0.015	−33.4 ± 16.7	<0.001
Peripheral DBP, mm Hg	−2.4 ± 9.5	0.354	−10.6 ± 10.5	<0.001
Peripheral PP, mm Hg	−0.3 ± 13.7	0.360	−21.7 ± 13.8	<0.001
Heart rate, beats/min	−4.4 ± 6.4	0.002	−2.8 ± 8.3	0.021
Central SBP, mm Hg	−0.9 ± 9.0	0.598	−29.4 ± 19.8	<0.001
Central DBP, mm Hg	−2.3 ± 9.6	0.449	−10.8 ± 11.4	<0.001
Central PP, mm Hg	−0.3 ± 14.4	0.602	−21.0 ± 15.0	<0.001
Augmentation, mm Hg*	−0.6 ± 6.2	0.446	−9.1 ± 8.2	<0.001
Augmentation index, %	−0.5 ± 8.1	0.425	−3.6 ± 5.6	0.005
Augmentation index @ 75 beats/min, %†	−2.3 ± 6.7	0.228	−4.5 ± 6.4	0.001
Ejection duration, % CL‡	−1.7 ± 3.5	0.030	−2.9 ± 3.1	0.001
Pressure-time integral, systolic, mmHg · s§	−159.3 ± 352.7	0.044	−617.5 ± 692.7	<0.001
PWV_{cf}, m/s	−1.4 ± 2.6	0.013	−1.8 ± 2.9	0.009

Values are mean ± SD. *Augmentation (ΔP) is the difference between maximal pressure and incident pressure at the first peak. †Augmentation index is proportion of the central pressure wave height attributable augmentation (ΔP) (AIx = (ΔP/PP) × 100) corrected for a heart rate of 75 beats/min. ‡Ejection duration was measured from start of waveform to closure of the aortic valve (see incision in Fig. 1) corrected for the cycle length (CL). §Systolic pressure-time integral is integration of the area under the central pulse pressure (PP) curve during ejection duration.
Abbreviations as in Table 2.

cardiac stress were also apparent in the group of patients with only minimal decrease of central pressures (Table 3). Whether this effect might translate into a clinical improvement of patients with heart failure with a preserved ejection fraction remains to be determined.

Study limitations. Our study has some potential limitations, including the lack of directly measured central hemodynamics. For obvious practical reasons central BP indices were derived from radial artery tonometry measurements.

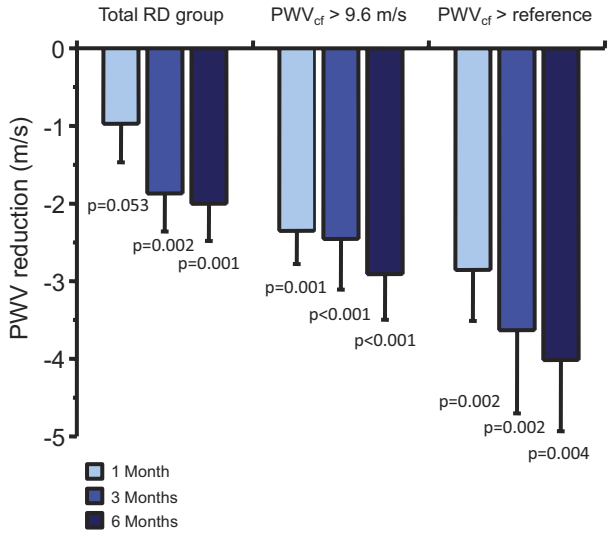

Figure 5 Effect of RD on PWV_{cf}

Change of carotid to femoral pulse wave velocity (PWV_{cf}) in the total renal denervation (RD) group, patients with PWV_{cf} >9.6 m/s at baseline, and patients with PWV_{cf} exceeding the double standard deviation of normal values of their age category 1, 3, and 6 months after RD. Values are presented as mean ± SEM and p values versus baseline.

The values for central aortic systolic and pulse pressures depend on the validity and applicability of the generalized transfer function used to generate the central aortic waveforms. Reassuringly, the correspondence between calculated and directly recorded central aortic systolic and pulse pressures has been found to be within 1 mm Hg (21,48). The transfer function used to derive the central aortic pressures is founded on the observation that pressure wave transmission in the upper limb is remarkably consistent under different conditions (16). This includes the effects of aging, disease, drug therapy, and variation in heart rate, thereby allowing the generalized transfer function to be used to convert the radial to an aortic pressure wave (22,48,49). Moreover, we chose to express PWV_{cf} values using the subtraction distance and intersecting tangent algorithm, which were shown to very accurately reflect invasive PWV measures (20–22,25,50). Given the lack of other therapeutic options for resistant arterial hypertension, we may not compare effects of RD with other treatment strategies. The control group is considerably smaller than the treatment group. Thus on the basis of harmonic means, the comparisons between treatment and control are equivalent to 2 groups of 18 subjects each, and the power for comparison of means is equivalent to two groups of 19. Because half of the treatment group has data at all the follow-up observations there is a resultant potential for bias if data might not be missing at random. The cohort in our study does not allow analysis of clinical outcome. Future results of this trial with longer follow-up and a larger cohort of treated patients will therefore be of interest.

Conclusions

Renal denervation offers a novel and safe catheter-based approach for selective reduction of renal sympathetic drive.

We demonstrated for the first time that selective denervation of the renal sympathetic nerves in addition to lowering peripheral BP significantly improves central hemodynamics in patients with resistant hypertension. Extrapolating from results of the CAFE (Conduit Artery Function Evaluation) trial (16), the effect on central hemodynamics documented in our study suggests a prognostic benefit of RD in patients with refractory hypertension, which should be evaluated in further trials.

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Key Words: arterial stiffness ■ central blood pressure ■ pulse wave velocity ■ renal denervation ■ resistant hypertension.